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☐ 1. Document ID: US 20020041876 A1

L3: Entry 1 of 7 File: PGPB Apr 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020041876
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020041876 A1

TITLE: TWEAK receptor

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wiley, Steven R.	Seattle	WA	US	

US-CL-CURRENT: 424/145.1; 424/178.1, 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020039992 A1

L3: Entry 2 of 7 File: PGPB Apr 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020039992
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020039992 A1

TITLE: Tek antagonists

PUBLICATION-DATE: April 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cerretti, Douglas P.	Seattle	WA	US	
Borges, Luis G.	Seattle	WA	US	
Fanslow, William C. III	Normandy Park	WA	US	

US-CL-CURRENT: 514/2; 424/130.1, 435/184, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20010026932 A1

L3: Entry 3 of 7 File: PGPB Oct 4, 2001

PGPUB-DOCUMENT-NUMBER: 20010026932
PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20010026932 A1

TITLE: CD40-binding APC-activating molecules

PUBLICATION-DATE: October 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thomas, David	Houston	TX	US	
Boer, Mark De	BT Blaricum		NL	
Res, Pieter C.J.M.	HC Haarlem		NL	
Simons, Peter J.	DH Hillegom		NL	

US-CL-CURRENT: 435/70.21; 424/144.1, 530/388.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6315998 B1

L3: Entry 4 of 7 File: USPT Nov 13, 2001

US-PAT-NO: 6315998
DOCUMENT-IDENTIFIER: US 6315998 B1

TITLE: Methods of blocking B-cell activation using anti-CD40 monoclonal antibodies

DATE-ISSUED: November 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Boer; Mark	Beuerwijk			NL
Conroy; Leah B.	Pacifica	CA		

US-CL-CURRENT: 424/144.1; 424/130.1, 424/133.1, 424/141.1, 424/143.1, 424/153.1, 424/173.1, 530/387.1, 530/387.3, 530/388.1, 530/388.2, 530/388.22, 530/388.7, 530/388.73

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6004552 A

L3: Entry 5 of 7 File: USPT Dec 21, 1999

US-PAT-NO: 6004552
DOCUMENT-IDENTIFIER: US 6004552 A

TITLE: Methods of blocking B cell proliferation using anti-CD40 monoclonal antibodies

DATE-ISSUED: December 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Boer; Mark	Beuerwyk			NL
Conroy; Leah B	Pacifica	CA		

US-CL-CURRENT: 424/144.1; 424/130.1, 424/133.1, 424/141.1, 424/143.1, 424/153.1, 424/173.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5874082 A

L3: Entry 6 of 7 File: USPT Feb 23, 1999

US-PAT-NO: 5874082
DOCUMENT-IDENTIFIER: US 5874082 A

TITLE: Humanized anti-CD40 monoclonal antibodies and fragments capable of blocking B cell proliferation

DATE-ISSUED: February 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Boer; Mark	Heemskerk			NL

US-CL-CURRENT: 424/153.1; 424/130.1, 424/133.1, 424/141.1, 424/143.1, 424/144.1, 424/173.1, 530/387.3, 530/388.22, 530/388.7, 530/388.73

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 5677165 A

L3: Entry 7 of 7 File: USPT Oct 14, 1997

US-PAT-NO: 5677165
DOCUMENT-IDENTIFIER: US 5677165 A

TITLE: Anti-CD40 monoclonal antibodies capable of blocking B-cell activation

DATE-ISSUED: October 14, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Boer; Mark	Beverwyle			NL
Conroy; Leah B.	Pacifica	CA		

US-CL-CURRENT: 435/343.1; 435/70.21, 530/388.22, 530/388.73

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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L2: Entry 27 of 62 File: USPT May 21, 2002

DOCUMENT-IDENTIFIER: US 6391637 B1
TITLE: Use of CD40 ligand, a cytokine that binds CD40, to stimulate hybridoma cells

Detailed Description Text (28):
Without being bound by theory, membrane-bound CD40-L and oligomeric CD40-L can achieve activity stimulating Ig formation and proliferation of B cells previously only achieved by cross-linked anti-CD40 antibody in the presence of IL-4. It further appears likely that monomeric soluble CD40-L, comprising only the extracellular domain of CD40-L and capable of binding to CD40 receptor, will serve to antagonize the activity of membrane-bound and oligomeric CD40-L and/or cross-linked anti-CD40 antibodies. It further appears likely that the interaction of membrane-bound CD40-L with CD40 is the principal molecular interaction responsible for T cell contact dependent induction of B cell growth and differentiation to both antigen specific antibody production and polyclonal Ig secretion. In this regard, a mammalian cell transfected with a cDNA encoding full length CD40-L (i.e., being membrane-bound and having an intracellular domain, a transmembrane region and an extracellular domain or a fragment thereof) can mimic T cells in their ability to induce B cell growth, differentiation and stimulation of antigen-specific antibody production. It appears that activities of oligomeric soluble CD40-L, preferably an oligomer of extracellular regions, can mimic the biological activities of membrane-bound CD40-L. Moreover, soluble monomeric CD40-L (comprising the extracellular domain or a fragment thereof) can bind to CD40 receptor to prevent T cell interaction with B cells and therefor have activity similar to CD40 (receptor) extracellular domain which itself may be in monomeric or in oligomeric form. Alternatively, CD40-L can be oligomeric to act as a soluble factor capable of inducing B cell growth, differentiation and stimulation of antigen-specific antibody production. Accordingly, it appears that membrane-bound CD40-L and oligomeric CD40-L act as CD40 agonists, while soluble (monomeric) CD40-L and soluble CD40 act as CD40 antagonists by blocking CD40 receptor sites without significantly transducing signal or by preventing CD40-L binding to CD40 sites on B cells and other target cells.

Detailed Description Text (29):
Both CD40 agonists and CD40 antagonists will have useful therapeutic activity. For example, CD40 agonists (i.e., membrane-bound CD40-L and oligomeric CD40-L) are useful as vaccine adjuvants and for stimulating mAb production from hybridoma cells. CD40 antagonists (i.e., CD40 receptor, CD40/Fc and possibly soluble, monomeric CD40-L) are useful for treating autoimmune diseases characterized by presence of high levels of antigen-antibody complexes, such as allergy, systemic lupus erythematosis, rheumatoid arthritis, insulin dependent diabetes mellitus (IDDM), graft versus host disease (GVHD) and others.

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((STIMULAT$ OR AGONIST$) SAME (CD40 OR 'G28-5')SAME(ANTIBOD$)).USPT.	173

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DATE: Sunday, August 25, 2002 Printable Copy Create Case

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L7	(stimulat$ or agonist$) same (cd40 or 'g28-5')same(antibod$)	173	L7
DB=PGPB; PLUR=YES; OP=ADJ			
L6	(stimulat$ or agonist$) same (cd40 or 'g28-5')same(antibod$)	74	L6
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L5	L4 and bispecific	51	L5
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L7: Entry 11 of 173 File: USPT Jul 2, 2002

DOCUMENT-IDENTIFIER: US 6413514 B1
TITLE: Methods of using antibodies against human CD40

Brief Summary Text (7):
The effects of in vivo inhibition of the CD40/gp39 interaction have been extensively studied in normal mice and mouse models of disease using a hamster anti-mouse gp39 mAb (MR1). The immunosuppressive capacity of the antibody is reflected in its ability to completely inhibit the humoral immune response to T-cell dependent antigens (Foy, et al., J. Exp. Med. (1993) 178:1567-75). Several mouse models of immune diseases have also been shown to be inhibited by treatment with the antibody, including those mediated by cellular immune responses. Disease models shown to be inhibited by treatment with anti-gp39 include collagen induced arthritis, experimental allergic encephalomyelitis, lupus nephritis, transplant rejection, and graft vs. host disease (Durie et al., Science (1993) 261:1328-30; Berry, et al., unpublished; Gerritse et al., Proc. Natl. Acad. Sci. USA (1995) 93:2499-504; Mohan et al., J. Immunol. (1995) 154:1470-1480; Larsen et al., Transplantation (1996) 61:4-9; Hancock et al., Proc. Natl. Acad. Sci. USA (1996) 93:13967-12; Parker et al., Proc. Natl. Acad. Sci. USA (1995) 92:9560-64; Durie, et al., J. Clin. Invest. (1994) 94:1333-38; Wallace, et al., unpublished). The role of CD40/gp39 in the amplification of a cellular immune response may be direct, through the stimulation of a subset of activated T cells that are capable of expressing CD40, or indirect, through induction of cytokines and the expression of important co-stimulatory cell surface molecules such as CD80 and CD86, which bind to the T cell receptors CD28 and CTLA-4. The anti-inflammatory effects of the inhibitor have been demonstrated by studies in a mouse model of oxygen-induced lung injury. The effects on inflammation in vivo are suggested by the in vitro results demonstrating stimulation of CD40 on vascular endothelial cells and monocytes which results in the expression of cell adhesion molecules, nitric oxide (NO), matrix metalloproteinases and proinflammatory cytokines (Kiener et al, J. Immunol. (1995) 155:4917-25; Malik et al., J. Immunol. (1995) 156:3952-60; Hollenbaugh et al., J. Exp. Med. (1995) 182:33-40).

Detailed Description Text (2):
The present inventors have developed an anti-human CD40 mAb with immunosuppressive properties. Such an anti-human CD40 mAb has obvious applications as a therapeutic. The present inventors have also developed a closely matched anti-mouse CD40 mAb (closely matched to the anti-human CD40 mAb) which is useful to study the effects of anti-CD40 mAb therapy in a number of mouse models of immune and inflammatory disease. Development of anti-CD40 antibodies is complicated by the fact that CD40 is a potent signaling molecule. Antibodies that bind to this antigen can be categorized based on the ability to stimulate CD40 signaling as well as the ability to block the CD40/gp39 interaction.

Detailed Description Text (10):
A panel of monoclonal antibodies was generated against human CD40 using standard hybridoma technology with human CD40 fusion protein as the immunogen. Antibodies were screened for binding to CD40 using both a CD40.sup.+ cell line and fusion proteins. Assays of gp39 binding to CD40 and functional assays of stimulation through CD40 were used to characterize cloned antibodies. Selected antibodies were then characterized for crossreactivity with primate cells to assess the suitability of the antibodies for use in primate preclinical models.

Detailed Description Text (48):
Based upon the results of in vitro assays (FIGS. 5a and 5b, that show both the

chimeric and humanized antibody effectively bound CD40 and inhibited B cell stimulation) the chimeric antibody was chosen for further study.

Detailed Description Text (82):
Following cloning, functional assays were performed with culture supernatants and purified antibody in order to more accurately assess the ability of the anti-CD40 mAbs to inhibit the interaction of murine gp39 with CD40 and to determine their stimulatory properties. Inhibitory properties were measured by the ability to inhibit the binding of mgp39 to WEHI-231 using standard procedures known in the art. Stimulatory properties were measured by the induction of tight, homotypic adhesion of WEHI-231 cells and the proliferation of splenic B cells in the presence of the antibody and anti-IgM using procedures known in the art. From these results, three mAbs (5A3, 7E1-G1 and 8E1) were determined to be most like the anti-human CD40 mAb2.220 with respect to gp39/CD40 blockade and level of costimulatory activity.

Detailed Description Text (84):
In vivo studies in mice were aimed at identifying which of the blocking/non-stimulatory anti-CD40 mAbs most potently suppressed specific antibody responses to a T-dependent antigen. Suppression of the IgG antibody response to SRBCs in mice with anti-murine CD40 mAb was studied. Groups of five BALB/c mice were immunized IV with 1.times.10.sup.8 SRBCs and concurrently treated ip with 1 mg of anti-murine CD40 mAbs 5A3, 7E1-G1 or 8E1. As controls, groups of similarly immunized mice were treated with MR1 (hamster anti-murine gp39, positive control, 250 ug), 6E9 (rat anti-human gp39, negative control, 1 mg) or PBS. Mice were evaluated for IgG anti-SRBC titers by ELISA on days 7, 14, 21 and 35. The results indicated that when administered as a single dose of antibody at the time of antigen challenge with SRBCs, mAb 7E1-G1 was shown to be a more effective suppressor of the IgG anti-SRBC response compared to mAbs 5A3 or 8E1, and was therefore selected as the lead anti-CD40 mAb for murine studies.

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L7: Entry 23 of 173 File: USPT Apr 9, 2002

DOCUMENT-IDENTIFIER: US 6368596 B1
TITLE: Compositions and methods for homoconjugates of antibodies which induce growth arrest or apoptosis of tumor cells

Brief Summary Text (11):
Recently it has been shown that MAbs can exert anti-tumor activity in other ways, e.g. by inhibiting metastases (Qi et al., 1995), tumor cell-substrata interactions (Guo et al., 1994), or tumor cell extravasation (Edward, 1995). In addition, it has been reported, that some MAbs can signal growth arrest and/or apoptosis of tumor cells, by acting as agonists ("negative signaling") (Ghetie et al.. 1992; Ghetie et al., 1994; Vitetta and Uhr, 1994; Trauth et al., 1989; Page and Defranco, 1988; Bridges et al., 1987; Funakoshi et al., 1994; Beckwith et al., 1991; Schreiber et al., 1992; Scott et al., 1985). "Negative signaling" is herein defined as the inhibition of cell growth by cell cycle arrest or the induction of apoptosis (programmed cell death). Indeed, in the case of B cell lymphoma, there is compelling evidence that both anti-idiotype (Levy and Miller, 1990; Hamblin et al., 1980) and anti-CD19 MAbs (Ghetie et al., 1992; Ghetie et al., 1994) exert their anti-tumor activities predominantly, if not exclusively, by signaling growth arrest and apoptosis. Other MAbs which also have signaling properties include anti-Fas (Trauth et al., 1989), anti-CD40 (Funakoshi et al., 1994); anti-Class II MHC (Bridges et al., 1987), anti-Her-2 (Scott et al., 1991), anti-Le.sup.y (Schreiber et al., 1992) and anti-IgM (Vitetta and Uhr, 1994; Page and Defranco, 1988; Beckwith et al., 1991; Scott et al., 1985). Furthermore, negative signaling can sometimes be optimized by hypercrosslinking with secondary antibodies or by using "cocktails" of primary antibodies (Marches et al., 1996).

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L7: Entry 35 of 173 File: USPT Oct 2, 2001

DOCUMENT-IDENTIFIER: US 6297052 B1
TITLE: B cell culture system comprising high density membrane bound CD40 ligand

Brief Summary Text (18):
The presently claimed methods improves previous attempts to proliferate B cells in the use of hdmb CD40 ligand. Previous attempts at proliferating B cell populations in the presence of naturally isolated membrane bound CD40 ligand, membrane bound CD40 ligand produced from transfected animal cells, recombinantly produced soluble forms of CD40 ligand, and anti-CD40 receptor antibodies has yielded poor results. Proliferation tends to be moderate, ending after 1-4 rounds of replication, and there is always a requirement for the presence of a lymphokine or cytokine (for example Th lymphokines) to stimulate proliferation. Using the present methods, proliferation responses as great as 250-fold, have been obtained.

Brief Summary Text (20):
A further embodiment of the present invention is based on the observation that cytokines, extracts from cells, and/or selected feeder cells when added to B cells which are proliferating or have been proliferated using the above described methods, stimulate the B cells to differentiate into antibody producing cells. Based on this observation, the present invention provides methods for differentiating proliferating B cells comprising the step of culturing B cells in the presence of hdmb CD40 ligand and one or more lymphokines, feeder cells, or extracts thereof. Examples of the cytokines and feeder cells which can be employed include, but are not limited to Th.sub.2 lymphokines and follicular dendritic cells.

Drawing Description Text (12):
FIG. 6. Growth and Antibody Secretion of B Cells Stimulated with hdmb CD40 ligand and D10 sn

Drawing Description Text (15):
FIG. 7. Growth and Antibody Secretion of B Cells Stimulated With hdmb CD40 Ligand and D10 sn With Medium Replacement

Detailed Description Text (22):
A further embodiment of the present invention is based on the observation that cytokines, extracts from selected cells, agents which crosslink surface receptors and Ig molecules, and/or selected feeder cell populations, when added to a B cells which are proliferating or have been proliferated using the above described methods, stimulate the B cells to differentiate into antibody producing cells. Based on this observation, the present invention provides methods for differentiating proliferating B cells which comprise the step of culturing B cells in the presence of hdmb CD40 ligand and a cytokine, feeder cells or extract thereof.

Detailed Description Text (64):
Initial characterization of the B cell activating molecules involved in delivering the contact signal to resting B cells came from biochemical studies on active Th cell membranes (Hodgkin et al., J. Immunol. 145:2025-2034 (1990)). By employing numerous washing, proteolysis, and detergent solubilization techniques, B cell activating molecules were found to be integral membrane proteins that required new mRNA and protein synthesis for their expression. In all respects B cell activating molecules were lymphokine-like components of the activated Th cell membrane: (Hodgkin et al., J. Immunol. 145:2025-2034 (1990)) they were synthesized de novo after Th cell activation; their synthesis by activated Th cells was rapid and

transient; and they exerted their effects on other cell types in a noncognate manner. In the first step towards identifying the B cell activating molecules, Lederman et al. isolated an antibody to a Th cell-specific molecule that exhibited all of the above characteristics (Lederman et al., J. Exp. Med. 175:1091-1101 (1992)). A simultaneous approach considered possible candidates for a constitutively expressed receptor for B cell activating molecules on the resting B cell surface. Several lines of evidence suggested that a probable B cell receptor for B cell activating was the CD40 molecule Stimulation of human B cells by antibodies to CD40 in the presence of lymphokines appeared to reproduce many of the features of Th-dependent B cell activation, proliferation, and differentiation (Jabara et al., J. Exp. Med. 172:1861-1864 (1990); Rousset et al., J. Exp. Med. 173:705-710 (1991); Zhang et al., J. Immunol. 146:1836-1842 (1991); Banchereau et al., Science 251:70-72 (1991)). CD40 belongs to the TNF receptor family whose members are characterized by repeated Cys-rich extracellular domains. By functional homology with TNF receptor a search for a soluble ligand for CD40 had been underway (Clark, E. A., Tiss. Antigens 35:33-36 (1990)). However, the activity of anti-CD40 antibodies and the ability of these antibodies immobilized on Fc receptor expressing L cells to induce long term human B cell growth (Banchereau et al., Science 251:70-72 (1991)) made it possible that a ligand for CD40 could be membrane-bound.

Detailed Description Text (65):
Several laboratories produced a soluble form of CD40 that linked the extracellular domain of human CD40 to the Fc portion of human IgG1 (Fanslow et al., J. Immunol. 149:655-660 (1992); Castle et al., J. Immunol. 151:1777-1788 (1993)). This fusion protein was capable of blocking Th cell-dependent B cell activation (Castle et al., J. Immunol. 151:1777-1788 (1993); Noelle et al., Proc. Natl. Acad. Sci. USA 89:6550-6554 (1992)) and was used to identify and clone a ligand for CD40 (Arinitage et al., Nature 357:80-82 (1992)). The CD40 ligand was identified as a 33,000-35,000 MW glycoprotein that was not covalently associated with other proteins and was expressed by activated T cells. When recombinant CD40 ligand was expressed on the surface of fibroblasts, it was capable of stimulating B cell proliferation, albeit at relatively low levels (Armitage et al., Nature 357:80-82 (1992)). Concurrently, antibodies were produced that recognized both human (Lederman et al., J. Exp. Med. 175:1091-1101 (1992)) and mouse (Noelle et al., Proc. Natl. Acad. Sci. USA 89:6550-6554 (1992)) B cell activating molecules. These antibodies had the property of blocking Th cell-dependent B cell activation events and were demonstrated to recognize the ligand for CD40.

Detailed Description Text (67):
Recent studies of several forms of recombinant human and mouse CD40 ligand have increased our understanding of the requirements of resting B cells for induction of activation and proliferation events. As a fusion protein with the extracellular domain of CD8.alpha., soluble CD40 ligand has been found to have a low level of activity for stimulating B cell proliferation (Lane et al., J. Exp. Med. 177:1209-1213 (1993); Hollenbaugh et al., EMBO J. 11:4313-4321 (1992)). In the absence of external crosslinking soluble CD40 ligand primarily acted as a costimulator of B cell proliferation in conjunction with phorbol esters, anti-CD20, or anti-.mu. (Lane et al., J. Exp. Med. 177:1209-1213 (1993); Hollenbaugh et al., EMBO J. 11:4313-4321 (1992)). We have observed that the CD8-CD40 ligand fusion protein is capable of driving resting B cell proliferation only after crosslinking with anti-CD8 or when used as a costimulator with Th2 lymphokines (B. Castle and M.R.K., unpublished observations). Because soluble CD40 is not monomeric (B. Castle and M.R.K., unpublished observations), this implies that resting B cells require a high degree of CD40 crosslinking for the induction of proliferation. Additionally, IL-4 appears to increase the sensitivity of resting B cells to low levels of CD40 crosslinking, as has been found using anti-CD40 antibodies (Clark, E. A., Tiss. Antigens 35:33-36 (1990); Rousset et al., J. Exp. Med. 173:705-710 (1991); Gordon et al., Eur. J. Immunol. 17:1535-1538 (1987)). Similar responses have been found using IL-4 and anti-.mu. antibodies (Hodgkin et al., Cell. Immunol. 134:14-30(1991)). Thus, under conditions that induce extensive crosslinking, CD40 ligand appears to be sufficient to activate resting B cells. Under suboptimal crosslinking conditions, CD40 ligand acts as a costimulator with lymphokines or other B cell surface molecules. Which conditions of B activation are similar to those induced by normal Th cells remains to be determined.

Detailed Description Text (75):
Because it has not been possible to keep normal untransformed B cells alive in vitro for extended periods of time, (Tisch et al., Immunol. Today 9:145-150 (1988)) the existing in vitro systems for studying B cell responses utilize freshly isolated B cells from spleen, tonsils, or peripheral blood. These B cell populations are inherently different and heterogeneous, and this variability may be responsible for many differing experimental results not only between different laboratories, but between mouse and human B cell studies. It has not been possible to establish B cell lines that are analogous to T cell clones (Tisch et al., Immunol. Today 9:145-150 (1988)). On the average, cultured B cells remain alive for less than 2 days in the absence of stimulation. Once activated in vitro by Th cells, B cells appear to undergo 2 to 3 rounds of cell division, and when Th2 lymphokines are present, they will differentiate to secrete antibody (Hodgkin et al., Eur. J. Immunol. (1994) in press). However, after the initial proliferation period, extensive B cell death occurs, so that actual viability after 7 days may be less than 10% (Hodgkin et al., Eur. J. Immunol. (1994)). This has made it impossible to establish in vitro systems for studying some of the poorly understood aspects of a B cell response: for example, signals that generate memory B cells and the molecular mechanisms that drive somatic mutation and selection of high affinity antibody producing cells. A system that utilized IL-4 and anti-CD40 antibodies immobilized on Fc receptor positive fibroblasts to grow human B cells for extended periods of time (Rousset et al., J. Exp. Med. 173:705-710 (1991); Banchereau et al., Science 251:70-72 (1991); Galibert et al., J. Immunol. 152:22-29 (1994)) has been the closest approximation to a B cell line. However, the cell doubling time was slow, (Galibert et al., J. Immunol. 152:22-29 (1994)), and the requirement for IL-4 generated antibody producing cells in the heterogeneous culture (Banchereau et al., Science 251:70-72 (1991)).

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L7: Entry 59 of 173 File: USPT Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6132978 A
TITLE: Method to regulate CD40 signaling

Drawing Description Text (5):
FIG. 4 illustrates the dose response of JNK activity to anti-CD40 antibody stimulation in tonsillar B cells treated for 15 min.

Detailed Description Text (34):
In another embodiment of the method of the present invention, cells suitable for use in the present invention are stimulated with a stimulatory molecules capable of binding to CD40 of the present invention to initiate a signal transduction pathway and create a cellular response. Preferably, cells are stimulated with a stimulatory molecule following contact of a putative regulatory compound with a cell. Suitable stimulatory molecules can include, for example, antibodies that bind specifically to the extracellular domain of CD40 and CD40 ligand. Preferred stimulatory molecules include, but are not limited to, anti-human CD40 antibody G28-5, soluble gp39, membrane-bound gp39 (e.g. gp39 bound to the plasma membrane of a cell or gp39 incorporated into a synthetic lipid-based substrate such as a liposome or micelle) and mixtures thereof. A suitable amount of stimulatory molecule to add to a cell depends upon factors such as the type of ligand used (e.g., monomeric or multimeric; permeability, etc.) and the abundance of the receptor on a cell. Preferably, between about 1.0 nM and about 1 mM of ligand is added to a cell.

Detailed Description Text (69):
JNK activity was measured by solid-phase kinase assay using GST-c-Jun (1-79) as a substrate following treatment with anti-IgM antibody or anti-CD40 antibody (G28-5) in Ramos cells (three independent experiments) and tonsillar B cells (two independent experiments). GST-c-Jun (1-79) fusion protein was purified from bacterial lysates using GSH-Sepharose beads (Pharmacia Biotech, Uppsala, Sweden) at room temperature with gentle rocking using the method described in Galcheva-Gargova et al. (Science 265:806-808, 1994). Following stimulation, 3.times.10.sup.6 cells were lysed in lysis buffer (20 mM Tris-HCl, pH 7.6, 250 mM NaCl, 3 mM EDTA, 3 mM EGTA, 0.5% NP-40, 2 mM Na.sub.3 VO.sub.4, 1 mM DTT, 1 mM PMSF, 20 .mu.g/ml aprotinin, 5 .mu.g/ml leupeptin). The lysates were mixed with 10 .mu.l of GST-c-Jun (1-79) coupled to GSH-Sepharose beads. The mixture was rotated at 4.degree. C. for 3 hr in a microcentrifuge tube and pelleted by centrifugation at 14,000 rpm for 5 min. The pelleted beads were washed 2 times in lysis buffer and once in kinase buffer (20 mM Hepes, pH 7.5, 20 mM .beta.-glycerophosphate, 10 mM MgCl.sub.2, 1 mM DTT, 50 mM Na.sub.3 VO.sub.4, 10 mM p-nitrophenyl phosphate), and then resuspended in 40 .mu.l of kinase buffer containing 10 .mu.Ci of [.gamma.-.sup.32 P]ATP. After 20 min at 30.degree. C., the reaction was terminated by adding 4.times. Laemmli sample buffer and boiling for 3 min. Samples were resolved by 12% SDS-PAGE and subjected to autoradiography. Phosphate incorporation was determined by PhosphorImager (Molecular Dynamics, Sunnyvale, Calif.). The level of .sup.32 P incorporation (.+-.SD) into the substrate is illustrated as the ratio of JNK activity to that of untreated samples.

Detailed Description Text (80):
Metabolically labeled (.sup.32 P)Ramos cells were untreated (control) or treated with 10 .mu.g/ml anti-IgM or 5 .mu.g/ml anti-CD40 for 1, 5 and 10 min, respectively. Ras was immunoprecipitated using the Y13-259 anti-Ras antibody, and radioactive GTP and GDP bound to Ras was measured as follows. Cells (10.sup.7 cells) were labeled with .sup.32 P-orthophosphate for 16 hr, and then stimulated. Ras was immunoprecipitated using the Y13-259 anti-Ras antibody, and GTP was separated from

GDP by thin layer chromatography as described (Downward et al., Nature 346:719-723, 1990). The radiolabeled nucleotides were visualized by autoradiography. Radioactivity was quantitated with a PhosphorImager and the GTP/GTP+(1.5) GDP ratios were calculated. The data were quantitated by PhosphorImager, and shown are the GTP/GDP+(1.5) GDP ratios (in percent) for each condition. The results represent three separate experiments. Statistically significant differences from untreated (0') samples are represented by an asterisk (*) ($p<0.05$).

Detailed Description Text (84):
Ramos cells were untreated or treated with 100 ng/ml PMA, 10 .mu.g/ml anti-IgM or 5 .mu.g/ml anti-CD40 for 1, 2.5, 5, 10 or 20 min. Raf-1 was immunoprecipitated and a kinase assay was performed using the following method. Cells (10.sup.7) were stimulated in RPMI 1640 medium, and then lysed in RIPA (10 mM sodium phosphate, pH 7.0, 150 mM NaCl, 2 mM EDTA, 1% sodium deoxycholate, 1% Nonidet P-40, 0.1% SDS, 1% aprotinin, 50 mM NaF, 200 mM Na.sub.3 VO.sub.4, 0.1% 2-mercaptoethanol, 1 mM PMSF). The lysates were precleared by protein A-Sepharose beads for 30 min at 4.degree. C. A purified polyclonal anti-Raf-1 antibody was added to the lysates (1:100; obtained from Santa Cruz Biotechnology, Santa Cruz, Calif.) and incubated for 90 min at 4.degree. C. The immunocomplexes were collected by protein A-Sepharose beads. The beads were then washed 3 times in RIPA and 3 times in a buffer containing 10 mM PIPES, pH 7.0, 100 mM NaCl, 2 .mu.g/ml aprotinin. A kinase mixture (40 .mu.l) containing 10 mM PIPES, pH 7.0, 100 mM NaCl, 5 mM MnCl.sub.2, 2 .mu.g/ml aprotinin, 30 .mu.Ci of [.gamma.-.sup.32 P]ATP and 100-200 ng of catalytically inactive MEK (KMMEK) was added to the beads. KMMEK was expressed and purified as described (Gardner et al., Methods Enzymol. 238:258-270, 1994). The samples were incubated for 30 min at 30.degree. C. The kinase reaction was stopped by addition of 4.times. Laemmli sample buffer and boiling for 3 min. The proteins were resolved on 10% SDS-PAGE and transferred to a nitrocellulose membrane. The membrane was probed using the same anti-Raf-1 antibody and visualized as described above and subjected to autoradiography.

Detailed Description Text (88):
Ramos cells were treated with 2 .mu.g/ml anti-CD40 antibody for 0, 0.5, 1, 2.5, 5 or 10 min. MEKK was immunoprecipitated and a kinase assay was performed using the following methods. Following stimulation, 5.times.10.sup.6 cells were lysed in 400 .mu.l of extraction buffer (1% Triton X-100, 10 mM Tris-HCl [pH 7.4], 5 mM EDTA, 50 mM NaCl, 50 mM NaF, 0.1% bovine serum albumin, aprotinin [20 .mu.g/ml], 1 mM PMSF, and 2 mM Na.sub.3 VO.sub.4). The lysates were centrifuged for 10 min at 14,000 rpm and pellets were discarded. The supernatants were incubated with the rabbit MEK kinase (MEKK) antisera (1:100 dilution) raised against the MEKK NH2-terminal fusion protein (described in Lange-Carter et al., Methods Enzymol. 255:290-301, 1995) for 2 hr at 4.degree. C. The immune complexes were collected by protein A-Sepharose beads. The beads were then washed twice in RIPA buffer and three times in a buffer containing 10 mM PIPES, pH 7.0, 100 mM NaCl, 2 .mu.g/ml aprotinin. A kinase mixture (40 .mu.l) containing 10 mM PIPES, pH 7.0, 100 mM NaCl, 5 mM MnCl.sub.2, 2 .mu.g/ml aprotinin, 30 .mu.Ci of [.gamma.-.sup.32 P]ATP and 0.5 .mu.l of recombinant JNK activating protein kinase (JNKK; described in Lin et al., Science 268:286-290, 1995) as a substrate was added to the beads. The samples were incubated for 30 min at 30.degree. C. The kinase reaction was stopped by addition of 4.times. Laemmli sample buffer and boiling for 3 min. The proteins were resolved on 10% SDS-PAGE, transferred to a nitrocellulose membrane and subjected to autoradiography. Phosphate incorporation was quantitated by PhosphorImager.

Detailed Description Text (89):
The results of .sup.32 P incorporation into JNKK are illustrated in FIG. 9 as the ratio of MEKK activity of treated to that of untreated samples. Statistically significant differences from untreated (0') samples are represented by an asterisk (*) ($p<0.05$). MEKK was activated rapidly, reaching maximal stimulation by 30 sec after anti-CD40 antibody treatment, and then decreased gradually with time. Immunoblots of the immunoprecipitated MEKK with the anti-MEKK polyclonal antibody that were used for immunoprecipitation revealed similar amounts of a 98 kD MEKK protein for each time point. These data indicate that an MEKK is present in B-lymphoblastoid cells which regulates the JNK pathway and is activated in response to CD40 ligation.

Detailed Description Text (92):
Ramos cells were untreated (control) or treated with 10 .mu.g/ml anti-IgM antibody or 2 .mu.g/ml anti-CD40 antibody; co-stimulation of cells consisted of a 30 min preincubation with anti-CD40 antibody followed by an incubation with anti-IgM antibody. After 18 hr culture, DNA breaks derived from anti-IgM induced apoptosis were evaluated using an in situ TdT assay using the method as follows. For detection of DNA strand breaks in individual cells, an in situ terminal deoxynucleotidyl transferase (TdT) assay was employed based on the method of Gorczyca et al. (Cancer Res. 53:3186-3192, 1993) with minor modifications. Cells were treated for 18 hr as indicated. About 10.sup.6 cultured cells were washed in PBS and suspended in 500 .mu.l of PBS. Paraform (4%, 170 .mu.l) was added and the mixture was stored on ice for 15 min. Cells were then washed in cold PBS and fixed with 70% ethanol at -20.degree. C. for an hour. Following washing in cold PBS, the cells were resuspended in TdT reaction buffer (0.1 M potassium cacodylate, pH 7.2, 2 mM CoCl.sub.2, 0.2 mM DTT, 20 U TdT, 2 nmol fluorescein-dUTP, 10 mg/ml BSA). After 30 min at 37.degree. C., cells were washed once in 0.2% BSA/PBS and fluoresce staining was evaluated on an EPICS Profile (Coulter, Hialeah, Fla.).

CLAIMS:

1. A method to identify a compound that regulates CD40 activation of Jun Kinase (JNK) in a cell, comprising:

(a) contacting a putative regulatory compound with a cell that expresses CD40 and Jun kinase;

(b) contacting said cell simultaneously or after said step (a) with a stimulatory compound selected from the group consisting of CD40 ligands, gp39, and antibodies that specifically bind to CD40, wherein said stimulatory compound stimulates CD40 signal transduction resulting in activation of Jun kinase, said contacting occurring under conditions in which, in the absence of said stimulatory compound, said Jun kinase is not activated;

(c) assessing the ability of said putative regulatory compound to regulate CD40-mediated activation of said Jun kinase, said activation being determined by measurement of an activity selected from the group consisting of phosphorylation of Jun kinase and phosphorylation of a substrate by Jun kinase;

wherein an increase or decrease in said activation of Jun kinase in the presence of said putative regulatory compound, as compared to in the absence of said putative regulatory compound, indicates that said compound regulates CD40-mediated activation of Jun kinase.

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L7: Entry 64 of 173 File: USPT Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117642 A
TITLE: Methods of determining disease activity in SLE patients by correlating the level of soluble CD40 ligand

Detailed Description Text (11):
Biological activity assays for use in the present invention measure cellular responses to the functional interaction of sCD40L with CD40, including without limitation: stimulation of B-cell proliferation; induction of B-cell surface activation, adhesion, and co-stimulatory molecules, such as, for example, CD23, CD54, CD80, CD86, CD95 and MHC Class II; B-cell stimulation of allogeneic T-cell proliferation; antibody production; immunoglobulin class switching; stimulation of endothelial cells or fibroblasts to express adhesion molecules; and stimulation of macrophages or dendritic cells to express cell surface activation molecules or cytokines such as interleukin-12. Typically, the biological activity of a sample is measured before and after incubation with neutralizing amounts of anti-CD40L antibody, and the difference between the two measurements reflects sCD40L-mediated activity.

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L7: Entry 131 of 173 File: USPT Sep 1, 1998

DOCUMENT-IDENTIFIER: US 5801227 A
TITLE: Antibodies to CD40

Brief Summary Text (5):
Monoclonal antibodies directed against the CD40 surface antigen have also been shown to mediate various biological activities on human B cells. For example, CD40 mAb induce homotypic and heterotypic adhesions (Barrett et al., J. Immunol. 146:1722, 1991; Gordon et al., J. Immunol. 140:1425, 1988), and increase cell size (Gordon et al., J. Immunol. 140:1425, 1988; Valle et al., Eur. J. Immunol. 19:1463, 1989). CD40 induce proliferation of B cells activated with anti-IgM, CD20 mAb, or phorbol ester alone (Clark and Ledbetter, Proc. Natl. Acad. Sci. U.S.A. 83:4494, 1986; Gordon et al., LEUCOCYTE TYPING III. A. J. McMichael ed. Oxford University Press. Oxford, p. 426; Paulie et al., J. Immunol. 142:590, 1989) or in concert with IL-4 (Valle et al., Eur. J. Immunol. 19:1463, 1989; Gordon et al., Eur. J. Immunol. 17:1535, 1987), and produce IgE (Jabara et al., J. Exp. Med. 172:1861, 1990; Gascan et al., J. Immunol. 147:8, 1991), IgG, and IgM (Gascan et al., J. Immunol. 147:8, 1991) from IL-4-stimulated T cell-depleted cultures. In addition, CD40 mAb have been reported to enhance IL-4-mediated soluble CD23/Fc.epsilon.RII release from B cells (Gordon and Guy, Immunol. Today 8:339, 1987; Cairns et al., Eur. J. Immunol. 18:349, 1988) and to promote B cell production of IL-6 (Clark and Shu, J. Immunol. 145:1400, 1990). Recently, in the presence of CD.sub.w 32+ adherent cells, human B cell lines have been generated from primary B cell populations with IL-4 and CD40 mAb (Banchereau et al., Science 241:70, 1991). Furthermore, germinal center centrocytes can be prevented from undergoing apoptosis if they are activated through CD40 and/or receptors for Ag (Liu et al., Nature 342:929, 1989). Each of the above publications describes CD40 mAb that stimulate a biological activity of B cells.

Detailed Description Text (39):
CD40.Fc or HuCD40-M2 were both shown to be able to inhibit CD40L-induced TNF-.alpha. production. Monocytes were stimulated with CD40L in the presence of GM-CSF. CD40.Fc and HuCD40-M2 were used at a final concentration of 10 .mu.g/ml. TNF-.alpha. was non-detectable (<5 .mu.g/ml) in control cultures with medium alone, GM-CSF alone, CD40L alone, CD40.Fc alone or CD40 antibody alone. FIG. 4 shows that in the absence of either CD40.Fc or HuCD40-M2, TNF-a production is stimulated with CD40L in the presence of GM-CSF. In contrast, both CD40.Fc and the CD40 blocking HuCD40-M2 inhibited TNF-.alpha. production induced by CD40L in the presence of GM-CSF. An isotype control mAb and human IgG1 were unable to block TNF-a production in this assay (data not shown). These data indicate that HuCD40-M2 specifically binds to a human CD40 molecule and is capable of blocking binding of the CD40 molecule to a CD40 ligand. These data further suggest that the HuCD40-M2 may be useful in blocking TNF-.alpha. mediated inflammation when used in conjunction with other cytokines.

Other Reference Publication (16):
Howard et al., Abstract "Antibodies to Murine CD40 Stimulate Normal B Cells But Inhibit Proliferation of B Lymphoma Cells," from Keystone Meetings, Jan./Feb. 1993.

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L5	L4 and bispecific	51	L5
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L8: Entry 22 of 32 File: USPT Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5985276 A
TITLE: Destruction of contaminating tumor cells in stem cell transplants using bispecific antibodies

Abstract Text (1):
The present invention discloses a procedure for the destruction of contaminating tumor cells in stem cell transplants ex vivo using intact bispecific antibodies.

Brief Summary Text (2):
The invention relates to the ex vivo destruction of contaminating tumor cells in stem cell transplants using intact bispecific antibodies.

Brief Summary Text (7):
For these reasons, other immunological approaches to purify the stem cell transplant were tested such as the addition of activated T cells in combination with bispecific F(ab')2 fragments to redirect T cells to the tumor cells in vitro. It turned out that by such purging hematopoietic stem cells are not affected in their function--as measured in proliferation assays--but the ability to kill tumor cells in these experiments was relatively limited (1-2 log tumor reduction). Also, the use of preactivated T cells cultivated for two weeks has to be regarded as a disadvantage of this approach forcing up the effort and hampering clinical application.

Drawing Description Text (3):
FIGS. 1A and 1B show the role of accessory cells in immunotherapy of tumors by means of bispecific antibodies (ADCC=antibody-dependent cell-mediated cytotoxicity).

Detailed Description Text (2):
Bispecific antibodies are able to bind to the T cell receptor complex of the T cell with one binding arm and to tumor-associated antigens on the tumor cell with the second binding arm. Thereby, they activate T cells which kill tumor cells by releasing cytokines. Moreover, there is the possibility that T cells recognize tumor-specific antigens via their receptor during activation by bispecific antibodies and that, thereby, a long-lasting immunization is initiated. Of particular importance in this regard is the intact Fc portion of the bispecific antibody which mediates the binding to accessory cells such as monocytes/macrophages/dendritic cells and causes these cells to become cytotoxic themselves and/or at the same time to transduce important co-stimulatory signals to the T cell (see FIG. 1).

Detailed Description Text (3):
In contrast to the prior art, according to the invention there are used intact bispecific antibodies. Intact bispecific antibodies are composed of two antibody semi-molecules (one H and one L immunoglobulin chain each) each representing a specificity, and in addition have like normal antibodies a Fc portion performing the well-known effector functions. They are preferably prepared using the quadroma technology. This method of preparation is exemplified in DE-A-44 19 399. For complete disclosure this document is incorporated in its entirety by reference. It should be understood that other methods of preparation are also useful if they lead to the intact bispecific antibodies according to the above definition required according to the invention.

Detailed Description Text (4):
In the method of the invention, contaminating tumor cells in stem cell preparations

(products of leucophoresis) are eliminated in vitro by means of bispecific antibodies (such as anti-CD3 X anti-c-erbB-2, anti-CD3 X anti-Lewis Y, and anti-CD3 X anti-Ep-CAM, for example anti-CD3 X anti-C215). Contacting the bispecific antibodies and the stem cells with the contaminating tumor cells is done under conditions that allow for binding of the bispecific antibodies to the tumor cells and the T cells as well as maintenance of the viability of the stem cells. To keep these parameters is necessary for the survival and the vitality of the stem cells and also of the lymphocytes. For example, the stem cell transplant (product of leucophoresis) is incubated for approximately 4-72 hours, preferably 24-48 hours, with bispecific antibodies at room temperature and a cell density of 30,000-75,000 cells/.mu.l, preferably 30,000-50,000 cells/.mu.l.with gentle shaking. With a total cell number of approx. 10.times.10.sup.9 cells/stem cell transplant, an amount of bsAb of 100-500 .mu.g is sufficient to kill the tumor cells. A further important point in the procedure of the invention is the use of so-called intact bispecific antibodies. These antibodies are not only able (due to the specificities employed herein) to direct T cells to tumor cells but due to the effector function of the Fc portion are also suitable to kill the tumor cells by complement-mediated lysis or by binding of Fc receptor-positive cells such as macrophages, monocytes or activated neutrophil granulocytes. Thus, by intact bsAb several mechanisms for tumor cell destruction can be activated at the same time.

Detailed Description Text (5):
The intact bispecific antibodies used in the present invention carry a functional Fc part. Contrary to bispecific F(ab)2 fragments which do not include a funtional Fc part the intact bispecific antibodies of the present invention are able to bind not only to T cells but also accessory cells which are also known as Fc-receptor positive cells (e.g. monocytes, macrophages, dendritic cells). The binding of the cells plays an essential role in providing an efficient direct tumor destruction which is 10-1000 times higher compared to the efficiency of the method used by Kaneko et al. The intact bispecific antibodies of the present invention enable an optimal co-stimulation of T cells directed to the antibodies by the accessory cells. In particular responsible for this optimal co-stimulation are surface antigens like CD40, B-7.1, B-7.2, LFA-3 and particular secreted cytokines (like IL-2, IL-6, IL-12, TNF-alpha).

Detailed Description Text (6):
By using the intact bispecific antibody of the present invention an efficient direct destruction of tumor cells by T cells is obtained and furthermore an immune response against the tumor is started. The accessory cells bound by the intact bispecific antibody of the present invention are stimulated to uptake, process and present parts of the tumor. These steps initiated by the use of the bispecific intact antibodies of the present invention are essentially responsible for the induction of a humoral and cellular immune response.

Detailed Description Text (7):
By using the intact bispecific antibodies in the method of the present invention not only a quantitive effect is obtained but also a new quality regarding the induction of an immune response against the tumor.

Detailed Description Text (8):
By using the intact bispecific antibodies of the present invention neither additional cytokines like IL-2 used for a pre-treatment of T cells nor a long lasting cultivation of these cells for at least two weeks is necessary. The cultivation of T cells has to-be conducted under particular conditions (GMP conditions) which are very costly and have to be done under authorization of Paul Ehrlich Institute or FDA. Cultivating of T cells under GMP conditions is not necessary in the present method. At present no other method is available to obtain an efficient destruction of tumor cells in stem cell transplants.

Detailed Description Text (18):
5. Destruction of contaminating tumor cells in the autologous stem cell preparation using bispecific antibodies (anti-CD3 x anti-c-erbB-2 and anti-CD3 x anti-Ep-CAM, 500 .mu.g/patient) by incubation for 24-48 h at room temperature and a cell density of 30,000-50,000 cells/.mu.l. Cryoconservation at -180.degree. C.

Detailed Description Text (24):
11. Administration of bispecific antibodies (200 .mu.g/1 mg/2 mg) in vivo in increasing dosage on three successive days accompanied by measures for prevention and treatment of anaphylactoid reactions.

Detailed Description Text (26):
Thus, according to the invention bispecific antibodies are employed for the reduction of the number of contaminating tumor cells for example of mammary carcinoma cells by destruction thereof in stem cell preparations. In this procedure, the antibodies function to redirect T cells to the vicinity of carcinoma cells and activate T cells to secrete cytokines such as tumor necrosis factor .alpha., leading to lysis of the tumor cell. By activation of macrophages via the Fc receptor located in the Fc portion of the bispecific antibody this cytokine effect is even enhanced; important co-stimulatory signals could be transmitted simultaneously to the T cell from the Fc.gamma.RI+ cell (monocyte/macrophage/dendritic cell) which prevent the anergizing of the T cell.

Detailed Description Text (27):
After transplantation has been performed bispecific antibodies are infused in increasing dosage following reinfusion of autologous T cells. Activation of T cells and lysis of residual mammary carcinoma cells is achieved in vivo. In this case, also tumor-specific T cells could be expanded (besides the stem cell preparation mentioned under 1) which up to then have been anergic due to partial stimulation at the tumor site via the T cell receptor without co-stimulus or due to IL-10 secretion by the tumor, respectively.

Detailed Description Text (29):
The preparation of bispecific antibodies is well known in the prior art. For example, intact bispecific antibodies may be produced in sufficient amounts using a newly developed method of preparation (2). The combination of two bispecific antibodies directed against two different tumor-associated antigens (e.g. c-erb-B2, Ep-CAM, such as GA-733-2=C215) on the mammary carcinoma cells minimizes the risk that tumor cells expressing only one of the antigens remain unidentified.

Detailed Description Text (31):
Because of the possible release of cytokines the bispecific antibodies are first administered in a low dosage and under strict control. According to reports in the literature similar bispecific antibodies were administered systemically in an amount of up to 13 mg without substantial side effects (1). Therefore side effects are hardly to be expected for a total amount of antibody of 4 mg/patient.

Detailed Description Text (32):
In the following the role of bispecific antibodies in the combination of chemotherapy and immunotherapy for the destruction of residual mammary carcinoma cells in the transplant and in the patient is described.

Detailed Description Text (43):
1. Weiner & De Gast, Bispecific monoclonal antibody therapy of B-cell malignancy, Leukaemia and Lymphoma, 1995, 16:199

Detailed Description Text (44):
2. Lindhofer et al, Preferential species-restricted heavy-light chain pairing in rat-mouse quadromas: Implications for a single step purification of bispecific antibodies, J. Immunology 1995, 155:219

Detailed Description Text (47):
5. Weiner et al., The role of T cell activation in anti-CD3 x antitumor bispecific antibody therapy, J. Immunology, 1994, 152:2385

Detailed Description Text (48):
6. Kaneko et al. Combination of IL-2 stimulated lymphocytes and bispecific antibodies that efficiently lyse leukemic cells does not affect bone marrow CD34-positive stem cell function in vitro. Bone Marrow Transpl.1994, 14:213

Detailed Description Paragraph Table (1):

TABLE 1 _____ Tumor colony growth assay Parental antibodies Bispecific Tumor cells/ No C215, anti- antibody BiUII MNCs/well Plate antibody CD3 anti-CD3XC215 (= 0.1%) _____ Patient 1 24 6/6.sup.a n.d. 0/6 .SIGMA. = 1.8 .times. 10.sup.7 3000/3 .times. 10e6 24 6/6 n.d. 0/6 1000/10e6 96 12/12 n.d. 0/12 500/5 .times. 10e5 96 10/12 n.d. 0/12 100/10e5 Tumor -- >4 log reduction: Donor 2 24 6/6 0/6 .SIGMA. = 3 .times. 10.sup.7 5000/5 .times. 10e6 24 6/6 n.d. 0/6 1000/10e6 96 12/12 n.d. 0/12 500/5 .times. 10e5 96 12/12 n.d. 0/12 100/10e5 Tumor -- -- >4.3 log reduction: Patient 3 24 6/6 6/6 2/6 4000/4 .times. 10e6 24 6/6 6/6 1/6 1000/10e6 96 12/12 12/12 0/12 500/5 .times. 10e5 96 12/12 12/12 0/12 100/10e5 Tumor -- -- 3 log reduction: _____ .sup.a Number of positive wells (tumor growth) of 6 or 12 sample wells, respectively, after a culture period of 14 days

CLAIMS:

1. A method for the reduction of the number of contaminating tumor cells in stem cell transplants ex vivo, comprising contacting stem cell transplants with intact bispecific antibodies capable of binding to the T cell receptor complex of a T cell, to the Fc-receptor of a Fc-receptor positive cell as well as to tumor-associated antigens on a tumor cell, under conditions that allow

said binding of said bispecific antibody to said tumor cells, T cells and Fc-receptor positive cells,

activation of said T cells by said antibody binding,

binding of said Fc-receptor positive cells to the Fc-region of said bispecific antibody

redirection of said T cells and Fc-receptor positive cells to said tumor cells,

destruction of said tumor cells by said activated T cells, and

ADCC killing of said tumor cells bv said Fc-receptor positive cells.

3. Method according to claim 1 in which said bispecific antibodies are members selected from the group consisting of anti-CD3 X anti-c-erbB-2antibodies, anti-CD3 X anti-Ep-CAM antibodies, and anti-CD3 X anti-Lewis Y antibodies.

4. Method according to claim 1 in which said stem cell transplant is contacted with the bispecific antibodies for a period of 4-72 hours.

5. Method according to claim 4 in which said stem cell transplant is contacted with said bispecific antibodies at a temperature of 20-25.degree. C.

9. Method according to claim 1 in which said stem cell transplant is contacted with the bispecific antibodies for a period of 24-48 hours.

10. Method according to claim 4 in which said stem cell transplant is contacted with said bispecific antibodies at room temperature.

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L8: Entry 30 of 32 File: USPT May 5, 1998

DOCUMENT-IDENTIFIER: US 5747037 A
TITLE: Anti-GP39 antibodies

Brief Summary Text (5):
A molecule, CD40, has been identified on the surface of immature and mature B lymphocytes which, when crosslinked by antibodies, induces B cell proliferation. Valle et al., Eur. J Immunol., 19:1463-1467 (1989); Gordon et al., J. Immunol., 140:1425-1430 (1988); Gruber et al., J. Immunol., 142: 4144-4152 (1989). CD40 has been molecularly cloned and characterized. Stamenkovic et al., EMBO J., 8:1403-1410 (1989). A ligand for CD40, gp39 (also called CD40 ligand or CD40L) has also been molecularly cloned and characterized. Armitage et al., Nature, 357:80-82 (1992); Lederman et al., J. Exp. Med., 175:1091-1101 (1992); Hollenbaugh et al., EMBO J., 11:4313-4319 (1992). The gp39 protein is expressed on activated, but not resting, CD4.sup.+ Th cells. Spriggs et al., J. Exp. Med., 176:1543-1550 (1992); Lane et al., Eur. J. Immunol., 22:2573-2578 (1992); Roy et al., J. Immunol., 151:1-14 (1993). Cells transfected with the gp39 gene and expressing the gp39 protein on their surface can trigger B cell proliferation and, together with other stimulatory signals, can induce antibody production. Armitage et al., Nature, 357:80-82 (1992); Hollenbaugh et al., EMBO J., 11:4313-4319 (1992).

Detailed Description Text (11):
The term antibody as used herein is intended to include fragments thereof which are specifically reactive with a gp39 protein or peptide thereof or gp39 fusion protein. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, F(ab').sub.2 fragments can be generated by treating antibody with pepsin. The resulting F(ab').sub.2 fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules having an anti-gp39 portion.

Detailed Description Text (96):
These studies indicate that when aGVHD is induced in mice, an anti-H-2.sup.d response is obtained. However, if the animals are treated with anti-gp39, then no CTL response is observed. It may be apparent that anti-gp39 is inhibiting the CTL formation by a method previously described (Schultz, K. R. et al. (1990) Science 249). The B cells fail to be activated via CD40 ligation and are thus unable to promote the induction of CTLs. Furthermore, our studies show that when spleen cells are challenged in vitro with P815 cells, the cells that were exposed to anti-gp39 in vivo were found unable to mount a secondary anti-H-2.sup.d CTL. Thus, this may indicate that anti-gp39 has induced a state of tolerance on the T cell compartment since gp39 is unable to engage CD40, there thus is no B7/BB1 upregulation and so the T cells do not get further activated and remain unresponsive. It is also known that resting B cells generally are ineffective stimulators of allogeneic T cells in the mixed lymphocyte reaction unless preactivated by anti-IgM antibodies, PMA or LPS (Inaba, K. and Steinman, R. M. (1989) J. Exp. Med. 160:1717; Metley, J. P. et al. (1989) J. Exp. Med. 169:239; Frohman, M. and Cowing, C. (1985) J. Immunol. 134:2269). In addition, soluble monomeric antigen directed to B cells for presentation in vivo may result in specific T cell anergy (Eynon, E. E. and Parker, D. (1992) J. Exp. Med. 175:131). Thus, it seems evident, depending on the method of administration of antigen and APCs involved, that anergy or tolerance may be induced. Upon challenge of P815 cells to the CD8+ T cells compartment of the spleen, B cells are not required for antigen presentation, thus alloantigen can be presented directly and CTL induced. The unresponsiveness of the spleens to secondary

stimulation indicates that allospecific tolerance has been induced in this system.

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CD40.DWPI,EPAB,JPAB.	228
CD40S	0
G28-5.DWPI,EPAB,JPAB.	4
G28-5S	0
STIMULAT$	0
STIMULAT.DWPI,EPAB,JPAB.	27
STIMULATAB.DWPI,EPAB,JPAB.	1
STIMULATABILITY.DWPI,EPAB,JPAB.	4
STIMULATABLE.DWPI,EPAB,JPAB.	33
STIMULATE.DWPI,EPAB,JPAB.	7628
STIMULATED.DWPI,EPAB,JPAB.	6934
((STIMULAT$ OR AGONIST$) SAME (CD40 OR 'G28-5')SAME(ANTIBOD$)).JPAB,EPAB,DWPI.	19

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DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L9	(stimulat$ or agonist$) same (cd40 or 'g28-5')same(antibod$)	19	L9
DB=USPT; PLUR=YES; OP=ADJ			
L8	L7 and bispecific	32	L8
L7	(stimulat$ or agonist$) same (cd40 or 'g28-5')same(antibod$)	173	L7
DB=PGPB; PLUR=YES; OP=ADJ			
L6	(stimulat$ or agonist$) same (cd40 or 'g28-5')same(antibod$)	74	L6
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L5	L4 and bispecific	51	L5
L4	(stimulat$ or agonist$) same (cd40 or 'g28-5')same(antibod$)	266	L4
L3	L2.clm.	7	L3
L2	(agonist$) same (cd40)same(antibod$)	62	L2
L1	thomas-david?	0	L1

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